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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/678,082
Filing Date: October 06, 2003
Appellant(s): LEMMENS ET AL.

Steven M, Reid
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/07/2010 appealing from the Office action mailed 05/11/2010.

(1) Related Appeals and Interferences

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has the following comment regarding the summary of claimed subject matter contained in the brief:

At page 7, 3rd paragraph of the brief, Appellant states the following:

> "Compositions in accordance with the appealed claims *exhibit surprising stability against the formation of a colored impurity that heretofore accompanied the formation of paroxetine sulfonate salt compositions*. See specification at page 3, lines 14-29." *Emphasis added.*

The stability against the formation of a colored impurity is not a property found in the subject matter of claims 51-59.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

6,113,944	PATHAK et al	9-2000
5,874,447	BENNEKER et al	2-1999
4,675,188	CHU	6-1987

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 51-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pathak et al (US 6,113,944 – "Pathak") in view of Benneker et al (US 5,874,447 – "Benneker") and Chu (US 4,675,188).

Pathak discloses paroxetine formulations for oral administration which are prepared by dry granulating in the absence of water. See column 1, lines 50-58 and column 2, lines 64-67. Conventional excipients used include calcium phosphate, sodium starch glycollate, and magnesium stearate. See column 2, lines 12-16. Working example 2 discloses a formulation comprising sodium starch glycollate, calcium phosphate, and magnesium stearate; microcrystalline cellulose, lactose or any other diluent or excipient is not included therein. Dry granulation is taught to overcome the recognized problem of discoloration in which paroxetine takes on a pink hue (column 1, lines 35-47).

Pathak differs from the instant claims insofar as it does not specify the use of sulfonate salts of paroxetine (it instead exemplifies the hydrochloride). It also does not specify the use of calcium hydrogen phosphate anhydrate in the form of plate shaped crystals or agglomerates thereof (= the commercially available product "A-Tab"). Instead, Pathak discloses the use of commercially available dicalcium phosphate dihydrates, i.e. "Emcompress" or "Ditab" (column 3, line 17).

Benneker et al teach that paroxetine sulfonate salts (such as paroxetine methane sulfonate) are preferable to paroxetine hydrochloride salts because the former do not undergo the discoloration associated with the latter when tableted, and because the former have better water solubility (and thus better bioavailability). See

column 1, lines 30-65. See also column 7, lines 8- 13 (teaching that either wet or dry granulation may be used). Excipients are only generally taught.

Chu teaches that thermally dehydrated dicalcium phosphates are preferred for use in direct compression tableting because they provide increased compressibility (column 2, lines 59-62), as compared to other conventional dicalcium phosphate products, including dibasic calcium phosphate dehydrate (column 1, lines 45-50). Additionally, Chu discloses that differences in pH can affect the shape and size of the crystals (col. 2, ll. 3-8). The pH can range from about 3 to neutral, i.e., 7, when boiling. Dehydration can cause the pH to drop but it can be neutralized after anhydrous formation. See column 3, lines 42-48. Paroxetine is not specifically disclosed.

It would have been obvious to have used a paroxetine sulfonate instead of hydrochloride in formulating the pharmaceutical compositions described by Pathak, motivated by the desire to further enhance discoloration resistance as taught by Benneker et al. Similarly, it would have been obvious to have thermally dehydrated the "Emcompress/Di-Tab" filler described by Pathak, in order to provide increased compressibility as taught by Chu. Dehydrating "Emcompress" or "Di-Tab" results in "A-Tab", the same product preferred by applicant.

Regarding claims 56-59, the pharmaceutical compositions suggested by the combined teachings of the Pathak and Benneker differ from the instant claims insofar as specific pH values are not provided. Generally, however, it is prima facie obvious to determine workable or optimal values within a prior art disclosure through

the application of routine experimentation. See *In re Aller*, 105 USPQ 233,235 (CCPA 1955); *In re Boesch*, 205 USPQ 215 (CCPA 1980); and *In re Peterson*, 315 F.3d 1325 (CA Fed 2003). Accordingly, it would have been obvious to have adjusted the relative percentages of the components suggested by the combined teachings of Pathak and Benneker to arrive at those pH values providing optimal performance for a particular given pharmaceutical formulation, per the reasoning of the cited precedent.

Furthermore, Chu provides that pH affects the size and shape of the dicalcium phosphate crystals and, therefore, provides an adjustable parameter that can be used to optimize the compressibility of tablets containing same.

(10) Response to Argument

A. Appellant's argument

Appellant argues that the rejection is founded on a factual error because the only pH discussed by Chu is that of a reaction medium from which calcium hydrogen phosphate anhydrate ("anhydrous CHP") is ultimately isolated. Apparently as support for this allegation, Appellant cites "Chu at col. 1, line 64 to col.2, line 8" and "col. 3, lines 42-48" (see footnote #12 at bottom page 10 of the appeal).

The Examiner submits that this is incorrect. There is no "reaction medium" from which anhydrous CHP is "isolated" as alleged by Appellant. The Examiner notes that Appellant's citation of "Chu at col. 1, line 64 to col.2, line 8 is misleading because that particular excerpt describes previous preparations of anhydrous CHP by others prior to

Chu as background information. Chu's method is described at col. 3, lines 42-48, and is reproduced below:

> "The porous anhydrous dicalcium phosphate can also be prepared by boiling a dicalcium phosphate dihydrate. Boiling can be conducting at pH's ranging from neutral to about 3. Dehydration will cause a *drop in pH of from 1 to 2 pH units*. The pH can be neutralized after anhydrous formation with a base, calcium bases such as lime being preferred." Chu, column 3, lines 42-48. *Emphasis added*.

Chu's CHP anhydrous is the product yielded when CHP dihydrate is dehydrated by heating according to Chu's method. This dehydration process used to form CHP anhydrous leads to a drop in the pH.

Apparently, the "reaction medium" Appellant is referring to is the dicalcium phosphate dihydrate ("CHP dihydrate") which is boiled (i.e., heated in a drier as outlined in working example 1 at column 6, lines 8-13) to yield the formation of anhydrous CHP and a drop in the pH by 1 to 2 units. From the excerpt, it is clear that CHP dihydrate is heated whether at a pH of about 3, 4, 5, 6, or neutral/7 and is converted to anhydrous CHP and apparently drops the resulting pH by 1 to 2 units as well. That is, drying CHP dihydrate yields a conversion to anhydrous CHP and a pH as low as about 1 to 2 or as high as 5 to 6[1]. The Examiner notes again that there is no mention of a "reaction medium" from which CHP anhydrous is isolated. The Examiner additionally refers to working example 1 described by Chu at column 6, lines 8-13 as additional evidence that CHP anhydrous is not isolated from a reaction medium.

> "Dicalcium phosphate dihydrate…was heated in a continuous rotary turbo tray drier for 2.5 hours at 180° C…[t]he thus formed anhydrous dicalcium phosphate was granulated…" Chu at column 6, lines 8-13.

Apparently, Appellant is attempting to suggest that another intermediate substance is formed after CHP dihydrate is heated and before the CHP anhydrous is formed in order to suggests that an intermediate substance is disclosed to have a pH value and not the CHP anhydrous itself. There is no mention by Chu of some other "substance"/"reaction medium" from which CHP anhydrous is isolated from as alleged by Appellant.

Appellant further alleges that even if it is assumed, *in arguendo*, that Chu does suggest a pH of its CHP product, there still remains no reasonable expectation that a composition comprising Chu's CHP product together with an active agent and other excipients would have a pH of 5.0 to 6.0. The Examiner disagrees. First the pH of CHP anhydrous ("CHP product" as described by Appellant) is clearly suggested by Chu as outlined above. Second, when CHP anhydrous having a pH within Chu's range (e.g., 5 to 6 – see above footnote #1), the pH of a composition would likely be altered to be made the same or similar to the CHP anhydrous. It is well within scientific reason that when an agent having an acidic pH is added to a composition, the composition's pH will likely be altered to be made the same or similar to the acidic agent's pH. As support for the scientific reasoning that the addition of Chu's CHP anhydrous compound to a composition would likely effect the pH as outlined by the Examiner, the Examiner cites

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[1] If CHP dihydrate is at an initial pH=7 and heated, then the resulting pH would drop 2 units to pH=5 or 1 unit to pH =6, the instantly claimed pH range. Similarly, if the initial pH is at the lowest pH disclosed for

Appellant's own specification where it is acknowledged that using "non-alkaline" CHP anhydrous compound[2], a pharmaceutical composition meeting the desired pH is attained. See instant specification, page 8, lines 5-7. Chu's CHP anhydrous having a pH of about 1, 2, 3, 4, 5 or 6 are "non-alkaline". The addition of Chu's "non-alkaline" CHP anhydrous compound would affect the pH of the composition as outlined above. Not only is the Examiner's position within scientific reasoning but it is also supported by Appellant's own specification.

For the above reasons, Appellant's claimed invention is rendered obvious by the prior art.

Even though the Examiner believes Chu very clearly suggests pH values for CHP anhydrous as outlined above, the Examiner, in arguendo, will provide an even clearer teaching of a pH value for CHP anhydrous below. Only for the purpose of provided an even clearer teaching of the pH for CHP anhydrous by Chu, the Examiner further notes that Chu provides the option to neutralize the pH (i.e., attain a pH of 7) of CHP anhydrous compound after the formation of the CHP anhydrous compound. See Chu at column 3, lines 46-48, i.e., the last sentence of the first excerpt reproduced above. This provides an even clearer teaching of a pH for CHP anhydrous that is 7. Appellant admits in the specification as outlined above that when "non-alkaline" CHP anhydrous (pH of 7 meets the scientific definition and Appellant's definition of "non-alkaline") is used, a pharmaceutical composition having Appellant's desired pH is attained. Accordingly, Appellant's assertion that Chu fails to teach or suggest a pH for

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Chu's method, about 3, then the resulting pH would be about 1 or about 2.

CHP anhydrous is incorrect and not persuasive as is Appellant's assertion that one of ordinary skill in the art would not reasonably expect CHP anhydrous to effect the pH of a composition in which it is incorporated.

Appellant criticizes the Examiner's reference to the instant specification.

The Examiner has not relied on Appellant's specification in order to make the obviousness rejection. The current specification is only used as additional evidence for the scientific reasoning that adding CHP anhydrous with a pH of 5 to 6 to a pharmaceutical composition would likely affect the pH of the composition to provide a similar pH.

It is further noted that Appellant does not provide any argument against whether one of ordinary skill in the art would have found it obvious to have thermally dehydrated the "Emcompress/Di-Tab" (i.e., dihydrate CHP) filler described by Pathak, in order to provide increased compressibility as taught by Chu. It is further noted that applicant does not provide any arguments against whether or not dehydrating "Emcompress" or "Di-Tab" in Pathak as suggested by Chu would result in "A-Tab" (i.e., CHP anhydrous), the same CHP anhydrous product preferred by applicant to attain the desired pH. Appellant focuses on whether or not a pH range would result when the composition of Pathak is modified as suggested by Chu. Accordingly, it is respectfully submitted that it is *prima facie* obvious to have modified Pathak as suggested by Benneker and Chu. Because it is clear that Chu discloses pH values for CHP anhydrous and because it is

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[2] "non-alkaline" CHP anhydrous apparently includes CHP anhydrous compounds having a pH of about 5.1 (instant specification at page 8, line 3), about 7, (*Id.*, line 5), and 6.1-7.2 (*Id.*).

clearly reasonable that Chu's CHP anhydrous would affect the pH of a pharmaceutical composition in which it is incorporated, the claimed pH range of 5 to 6 is met.

For all of the above reasons, Appellant's claimed invention is rendered obvious by the prior art.

B. *Appellant's argument*

Appellant argues that the Examiner "erred by relying upon inherency" in the context of the rejection. Appellant also states that "[t]he Office action does not invoke the term 'inherency'" (see appeal page 12, footnote #14).

The prior art suggests every ingredient including the excipients currently claimed in independent claims 51 and 56, The Appellant acknowledges that the excipients, with particular emphasis on CHP anhydrous, are used to adjust the pH of the final composition. Appellant acknowledges in the specification at page 8, lines 6-11 that "using a non-alkaline calcium phosphate as an excipient, a pharmaceutical composition meeting the desired pH can be attained. Alternatively, a blend of calcium phosphates, even one using acidic and alkaline calcium phosphates, can be used to achieve the desired acidic pH of the composition. The pH can also be assisted by selection of any other excipients in the composition. For instance, another example of a useful acidic excipient is the disintegrant Explotab™ of Penwest, which is a cross-linked, low substituted sodium starch glycollate."

Because every ingredient in the claimed compositions would be present in the composition suggested by the prior art – e.g., A-Tab (see above rejection where Chu

suggests dehydrating calcium phosphate) and Explotab™ (see working example in Pathak, column 3, line 19) – the pH would likely be the same or similar to the pH being claimed as it is the presence of these ingredients that would provide the resulting pH of the composition. Appellant even acknowledges that the presence of Explotab™ as an excipient helps to adjust the pH within the ranges of the present invention. See instant specification at page 7, lines 25-26 and page 8, lines 9-11.

It would appear that Appellant's current argument contradicts the instant specification where it expressly states that the presence of certain ingredients, excipients such as A-Tab™, non-alkaline CHP anhydrous, and Explotab™ can be used to provide the pH ranges of the present invention. However, it now appears Appellant is taking the position that the presence of the same ingredients in the composition suggested by the prior art does not at the least reasonably suggest a similar pH ranging from 5.0 to 6.0.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/CHRIS SIMMONS/

Examiner, Art Unit 1612

Conferees:

/MICHAEL G. HARTLEY/

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